Aliphatic nitro compounds in stereoselective synthesis

Aken, Everhard van

CHAPTER V

AN ACHIRAL BICYCLIC AMIDINE AND GUANIDINE AS MODEL CATALYST

V 1 INTRODUCTION

The acyclic and monocyclic geminal dinitrogen bases, described in chapter 4, exhibit too low catalytic activity in the nitroalkane Michael reactions. The bicyclic guanidines, as described in this chapter, proved better catalysts in the nitroalkane addition reactions. In addition, in contrast to the relatively flexible acyclic and monocyclic bases, the bicyclic structure maintains the geminal dihydrogen bond donating functionality in a fixed conformation, limiting the topological freedom of the cation/nitronate anion complex as depicted in figure 5.1.

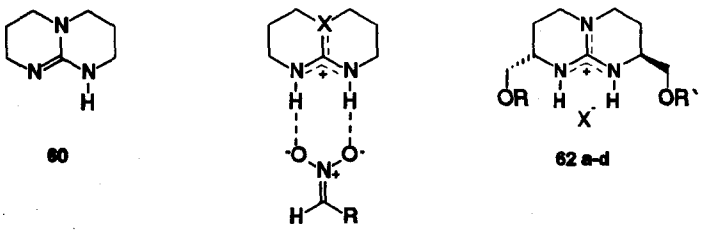


Figure 5.1 *The bicyclic guanidine TBD* **60**, *a proposed structure of a comoplex of a bicyclic amidininium X = CR or guanidinium X = N cation and a nitronate anion and the bicyclic guanidinium salts: R=R'=H* **62a**, *R=R'=naphthoyl* **62b**, *R=R'=CH_2OCH_3 (-MOM)* **62c** *and R=naphthoyl, R'=crown ether* **62d**.

In this chapter the catalytic activities of the achiral bicyclic guanidine TBD **60** and the pentamethylbicyclic amidine PMBA **61a** in the nitroalkane Michael and Henry reactions are described. In the second part of this chapter, the mode of complexation, as proposed in figure 5.1 between a bicyclic geminal dinitrogen base and a nitroalkane substrate, is established by an X-ray crystal structure of such a salt. NMR spectroscopy experiments show that the proposed structure probably also exsists in solution.

V 1.1 Anion complexation by bicyclic amidines and guanidines

Bicyclic amidines as well as guanidines have been used to complexate anions. Eschenmoser and co-workers reported the complexation of carboxylate, phosphate and

sulfate anions by the pentamethylbicyclic amidine (PMBA) **61a**[1] (figure 5.2).

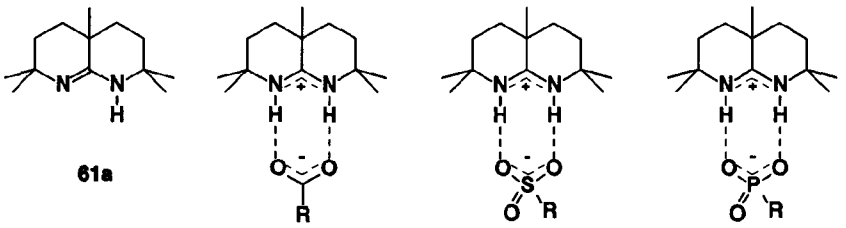


Figure 5.2 *Anion complexes with the Eschenmoser bicyclic amidine* **61a**.

The bicyclic guanidine functionality has been applied more often to complex anions than the amidine analog. Complexations with phosphate,[2] carboxylate[3] and nitrate[4] anions have been reported. Recently, receptors based on the bicyclic guanidinium salts **62a** were reported to specifically complex adenosine monophosphates,[5] and dinucleotides.[6]

V 1.2 Enantioselective anion complexation

The chiral bicyclic guanidinium salt **62a**, prepared by Mendoza and co-workers[7] was designed for stereoselective complexation. Some stereoselectivity was observed in the complexation of *N*-acetyltryptophane with the dinaphthoyl derivative **62b**.[3a] The R=mononaphthoyl and R'=monocrownether derivative **62d** was used in extraction experiments to differentiate between the two enantiomers of tryptophane and phenylalanine.[8] The proposed complex with tryptophane is shown (figure 5.3). The amino acids were extracted with e.e.'s larger than 90 %. The high enantioselective

---

1 Heinzer, F.; Soukup, M. and Eschenmoser, A., *Helv. Chim. Acta* **1978**, 61, 2851.

2 (a) Schmidtchen, F.P., *Tetrahedron Lett.* **1989**, 30, 4493. (b) Schmidtchen, F.P.; Gleich, A. and Schummer, A., *Pure Appl. Chem.* **1989**, 61, 1535. (c) Galán, A.; Pueyo, E.; Salmerón, A. and de Mendoza, J., *Tetrahedron Lett.* **1991**, 32, 1827.

3 (a) Echavarren, A.; Galán, A.; Lehn, J.-M. and de Mendoza, J., *J. Am. Chem. Soc.* **1989**, 111, 4994. (b) Schmidtchen, F.P.; Gleich, A. and Schummer, A., *Pure Appl. Chem.* **1989**, 61, 1535. (c) Müller, G.; Riede, J. and Schmitchen, F.P., *Angew. Chem.* **1988**, 100, 1574.; ibid *Int. Ed. Engl.* **1988**, 27, 1516.

4 Gleich, A.; Schmidtchen, F.P.; Mikulcik, P. and Müller, G., *J. Chem. Soc., Chem. Commun.* **1990**, 55.

5 (a) Galán, A.; Puyeo, E.; Salmerón, A. and de Mendoza J., *Tetrahedron Lett.* **1991**, 32, 1827. (b) Deslongchamps, G.; Galán, A.; de Mendoza J. and Rebek, Jr., J., *Angew. Chem., Int. Ed. Engl* **1992**, 31, 61.

6 Galán, A.; de Mendoza J.; Toiron, C.; Bruix, M.; Deslongchamps, G. and Rebek, Jr., J., *J. Am. Chem. Soc.* **1991**, 113, 9424.

7 Echavarren, A.; Galán, A.; de Mendoza, J.; Salmerón, A. and Lehn, J.-M., *Helv. Chim. Acta* **1988**, 71, 685.

8 Galán, A.; Andreu, D.; Echavarren, A.M.; Prados, P. and de Mendoza, J., *J. Am. Chem. Soc.* **1992**, 114, 1511.

extractions were explained by a three point interaction between the guanidinium host and the amino acid guests.

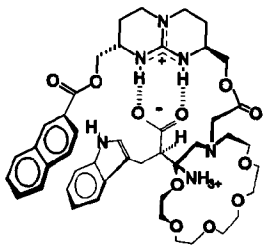


Figure 5.3 *The proposed complex between the (S,S)-guanidinium* **62d** *and L-tryptophane.*

The carboxylate complexes with the guanidinium moiety, the indole unit is thought to interact via π-π interaction with the naphthoyl group of the host molecule **62d** and the ammonium group is proposed to bind to the crown ether unit. This type of complex resembles the three point interaction between a chiral catalyst and two substrates as shown in figure 1.12 (section I 4.3).

V 1.3 The working hypothesis

The desired catalyst substrate complex is given in figure 5.4.

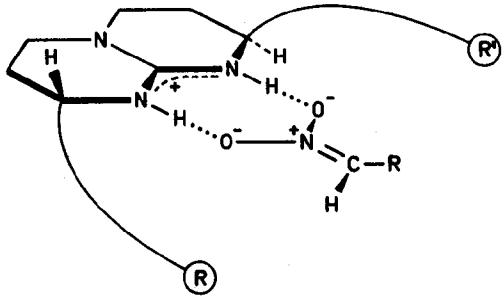


Figure 5.4 *A proposed guanidinium catalyst/nitronate complex.*

The achiral nitroalkane is deprotonated; the prochiral nitronate anion **8** is formed. The binding mode between the anion and the cation is independent of the different substituents R and R' of the guanidinium catalyst. Ideally, the catalytic activity of the catalyst remains while the selectivity of the catalyst can be altered by changing the two groups R or R'. A predictable binding mode between the catalyst and the nitroalkane substrate is combined with the possibility to change the peripheral structure of the catalyst.

V 2 1,5,7-TRIAZABICYCLO[4,4,0]DEC-5-ENE (TBD) AS AN ACHIRAL MODEL CATALYST[9]

TBD **60** as a model catalyst[10] was tested for its catalytic activity and complexation ability. TBD **60** is a hundred times more basic then tetramethylguanidine **45**[11] and from experiments we observed that the guanidine **60** is much better soluble in toluene then quinine **1a**.

V 2.1 TBD as a catalyst in the Michael reaction

TBD **60** was tested as a catalyst in six nitroalkane Michael reactions using MVK **13** as acceptor yielding **14a-14h** (table 5.1). The reactions were performed under standard conditions (0.1 M in toluene at room temperature). After one night some oil, probably some TBD:nitronate salt, had separated at the bottom of the flasks. The work-up procedure is identical to that of the cinchona alkaloid catalyzed reactions (section II 8).

Table 5.1 TBD **60** *as the catalyst in nitroalkane Michael reactions.*[a]

nr	product	Time hrs	c.y. %
1	**14a**	16	54[b]
2	**14b**	16	69[b]
3	**14c**	16	82
4	**14f**	20	86
5	**14g**	20	75
6	**14h**	20	83[c]

(a) All reactions were run at 0.1 M; the nitroalkanes were used in a fourfold excess, 0.4 M; 10 % TBD **60** was added. (b) Some losses may have occurred during the evaporation of toluene. (c) Chemical yield after distillation.

To obtain a quantitative comparison between the catalytic activity of TBD **60** and that of quinine **1a**, the reactions were followed by GC analysis. The results are given in figure 5.5. TBD **60** is a much better catalyst than quinine **1a** in the nitroalkane Michael reactions. Its catalytic activity allows overnight experiments at low enough concentrations of 0.1 M (see chapter 2).
TBD **60** is a strong base, capable of deprotonating secondary nitroalkanes, probably prone to racemize secondary nitroalkane products under reaction conditions. Optically enriched Michael adduct 5-nitro-2-hexanone **14b** ($[\alpha]^{rt}_{365}$ = -7.0°; 72.5 mg; 0.50 mmol) was dissolved in 10 ml of toluene (0.05 M). Three equivalents of nitroethane **12b**, one equivalent of benzene and 3.5 mg (0.025 mmol; 5%) of the catalyst **60** were added. The product was worked up after stirring for 5 hours at room temperature. The Michael adduct was recovered in 92 % and had lost all optical activity. Thus, guanidine base **60** racemizes the secondary nitroalkane **14b** under reaction conditions.

---

9 TBD **60** is commercially available; Fluka, 1,5,7-Triazabicyclo[4,4,0]dec-5-ene (TBD), nr 90605.

10 McKay, A.F. and Kreling, M.-E., *Can. J. Chem.* **1957**, 35, 1438.

11 Schwesinger, R., *Chimia* **1985**, 39, 269.

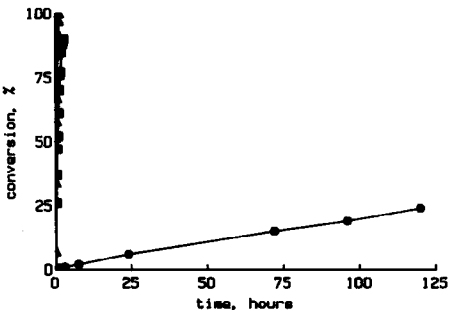


Figure 5.5 *TBD* **60** *as a catalyst in the standard reaction I (■) ; the standard reaction II (▲) ; and quinine* **1a** *(●) as the catalyst in the standard reaction I.*

V 2.2 TBD 60 as a catalyst in the Henry reaction

The Henry reaction is a classical bond forming process in organic chemistry; the reaction has not been applied extensively in synthesis because of the lability of the β-nitro alcohol products. Recently, a relatively easy procedure of a series of Henry reactions was published.[12] One equivalent of triethylamine, 1.5 eq. of trialkyl silylchloride and 0.25 eq. of n-$Bu_4NF.3H_2O$ as the catalyst were needed to obtain reasonable yields. TBD **60** was tested as the catalyst in a comparable series of Henry reactions. Aldehydes were added to a fourfold excess of the nitroalkane, to which, relative to the aldehyde, 5 mol % TBD **60** was added. The results are collected in the tables 5.2 - 5.4.

Nitroethane **12b** was reacted with a series of aldehydes **69 a-h** (table 5.2). The reactions with sterically unhindered aldehydes aromatic as well as aliphatic resulted in high conversions at short reaction times. The reactions ran to completion within minutes.

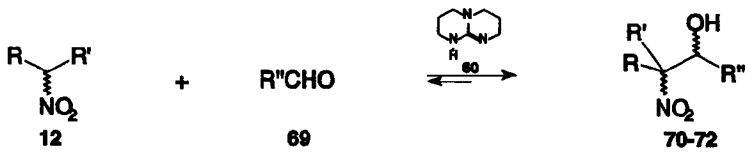
The sterically more hindered aldehydes reacted considerably slower. E.g., the addition of nitroethane **12b** to pivaldehyde **69e** (entry 5) resulted in a conversion of only 44 % after 18 hrs of reaction time. The diastereoselectivities increased a little with the size of the aldehyde group R" (entries 1-5). The aromatic aldehydes resulted in somewhat higher diastereoselectivities compared to the aliphatic aldehydes (entries 6-8).

A series of nitroalkanes was reacted with valeraldehyde **69c** (R"=n-C_4H_9) under the conditions described above (table 5.3). A small increase in the diastereoselectivities is shown with an increasing size of the nitroalkane R substituent (entries 10-12). The addition of phenylnitromethane **12f** to valeraldehyde **69c** resulted in the highest diastereoselectivity in these series (entry 14). Secondary nitroalkanes react a little more sluggish (entries 15 and 16) than the primary nitroalkanes. During these longer reaction times small amounts (<5 %) of aldol adduct were formed.

---

12 Fernández, R; Gasch, C; Gómez-Sánchez, A. and Vílchez, J.E., *Tetrahedron Lett.* **1991**, 32, 3225.

Table 5.2 TBD **60** *as catalyst in Henry reactions of nitroethane.* **12b** *and a series of aldehydes.*[a]



nr	prod.	R 12b	R'	R" 69a-h	Time min	conv.[b] %	c.y.[c] %	d.e.[d] %
1	**70a**	CH_3	H	**69a** CH_3	<2	100	71	-
2	**70b**	CH_3	H	**69b** n-C_3H_7	<2	100	95	13
3	**70c**	CH_3	H	**69c** n-C_4H_9	<2	100	99	11
4	**70d**	CH_3	H	**69d** i-C_4H_9	10	100	100	17
5	**70e**	CH_3	H	**69e** t-C_4H_9	18 hr	44	44	31
6	**70f**	CH_3	H	**69f** C_6H_5	5	90	90[e]	25
7	**70g**	CH_3	H	**69g** C_4H_4O(furyl)	15	91	88[e]	42
8	**70h**	CH_3	H	**69h** *o*-OH(C_6H_4)	18 days	35	30[e]	40

(a) The reaction, as given in tables 5.2 - 5.4, were run at ambient temperature, without solvent and with 5 % TBD **60** as the catalyst. The ß-nitro alcohols were isolated by filtration over silicag (Merck 60) and evaporation of the excess of reagents. (b) Determined by ^{1}H NMR. (c) Direct work up unless stated otherwise. (d) Determined by ^{13}C NMR (e) After removal of the unreacted aldehyde.

Table 5.3 TBD **60** *as catalyst in a series of Henry reactions with valeraldehyde* **69c**.

nr	prod.	R 12a-h	R'	R" 69c	Time min	conversion[a] %	c.y.[b] %	d.e.[c] %
9	**71a**	H	H	n-C_4H_9	15	100	98	-
10	**71b**	CH_3	H	n-C_4H_9	15	100	98	11
11	**71c**	CH_3CH_2	H	n-C_4H_9	15	100	98	13
12	**71d**	$CH_3CH_2CH_2$	H	n-C_4H_9	15	100	99	27
13	**71e**	$(CH_3)_2CHCH_2$	H	n-C_4H_9	15	>95	100	24
14	**71f**	C_6H_5	H	n-C_4H_9	15	10	91[d]	70
15	**71g**	CH_3CH_2	CH_3	n-C_4H_9	15	49	95[d,e]	20
16	**71h**	$CO_2C_2H_5$	CH_3	n-C_4H_9	15	29	81[e,f]	nd

(a) Determined by ^{1}H NMR. (b) Direct work up unless stated differently. (c) Determined by ^{13}C NMR (d)Work-up after one day. (e) Contained some aldol adduct (less than 5 %). (f) Work-up after one day and after distillation.

The nitroalkanes **12a-c** and **12e-h** were reacted under the same conditions with the sterically more demanding 2-methylpropanal **69i**. The results are collected in table 5.4. The addition reactions of the nitroalkanes **12a-c** and **12e-h** to the α-substituted aldehyde **69i** (table 5.4) were somewhat slower than the additions to valeraldehyde **69c** (table 5.3). Again the diastereoselectivities increased a little with an increasing size of the group R (entry 19 vs. 18). Phenylnitromethane **12f** with an aromatic group resulted in the highest diastereoselectivity (entry 21). The sterically congested *sec*-nitroalkanes **12g** and **12h** resulted in practically no conversion to the ß-nitro alcohol (entries 22 and 23), under the used reaction conditions. No catalysis was found with TBD **60** as the catalyst in the addition of nitroalkanes to ketones either, under the conditions applied.

Table 5.4 TBD **60** *as the catalyst in a series of Henry reactions with 2-methylpropanal* **69i**.

nr	product	R **12a-c,e-h**	R'	R" **69i**	Time min	conv. %	c.y.[a] %	d.e.[b] %
17	**72a**	H	H	$CH(CH_3)_2$	30	95	100	-
18	**72b**	CH_3	H	$CH(CH_3)_2$	30	75	100	14
19	**72c**	CH_3CH_2	H	$CH(CH_3)_2$	30	90	100	42
20	**72e**	$(CH_3)_2CHCH_2$	H	$CH(CH_3)_2$	30	80	100	39
21	**72f**	C_6H_5	H	$CH(CH_3)_2$	30	19[c]	90[d]	54
22	**72g**	CH_3CH_2	CH_3	$CH(CH_3)_2$	30	0	0	-
23	**72h**	$CO_2C_2H_5$	CH_3	$CH(CH_3)_2$	30	0	0	-

(a) Work up after 16 hrs unless stated differently. (b) Determined by ^{13}C NMR. (c) Conversion raised from 19% (30 min); 38%(1 day); 75%(2days); 95%(5 days). (d) Work up after 6 days.

In all reactions almost no aldol adducts were formed. The diastereoselectivities of the TBD **60** catalyzed Henry reactions are comparable to those reported.[13] The diastereoselectivities are higher when aromatic groups are used in the aldehyde and/or in the nitroalkane substrates. The stereochemical difference between a proton and a aromatic group is larger than the difference between a proton and an aliphatic substituent. The threo diastereoisomers were formed in excess in all cases, determined by ^1H-NMR.[14] For the aliphatic compounds the threo and erythro assignments were based on chemical shift differences between the ^1H-NMR signals of the compounds.
In conclusion, one can say that for the TBD **60** catalyzed Henry reactions our experimental procedure to the ß-nitroalcohols is far more convenient then any other procedure reported so far. TBD **60** as the catalyst in the nitroalkane additions to unsubstituted aldehydes resulted in short reaction times in combination with a very simple work-up procedure.

V 2.3 TBD 60 in complexation experiments with nitroalkanes

TBD **60** was used as a model to study the mode of complexation between nitroalkanes and guanidine or amidine bicyclic bases.

V 2.3.1 NMR experiments

The ^1H-NMR spectrum of a 1:1 complex (figure 5.6) and a NOE spectrum of phenylnitromethane **12f** and TBD **60** are described.
A 0.025 M solution of a 1:1 mixture of phenylnitromethane **12f** and TBD **60** in deuterated benzene was prepared. A complete proton transfer, on the NMR time scale was observed (figure 5.6). All signals of the aromatic ring became distinct, not ruling out, however, rotation around the C_1-Cα bond of **12f**.

13 (a) Barrett, A.G.M.; Robyr, C. and Spilling, C.D., *J. Org. Chem.* **1989**, 54, 1233. (b) Fernández, R; Gasch, C; Gómez-Sánchez, A. and Vílchez, J.E., *Tetrahedron Lett.* **1991**, 32, 3225 and references therein.

14 The threo compounds result in higher coupling constants (J=6Hz) then the erythro isomers (J=4.5 Hz). The coupling constants of only some of the aliphatic ß-nitroalcohols could be determined, because of smaller shift differences and more complex coupling patterns. (a) Seebach, D.; Beck, A.K.; Lehr, F.; Weller, Th. and Colvin, E.W., *Angew. Chem.* **1981**, 93, 422. (b) Seebach, D.; Beck, A.K.; Mukhopadhyay, T. and Thomas, E., *Helv. Chim. Acta* **1982**, 65 1101.

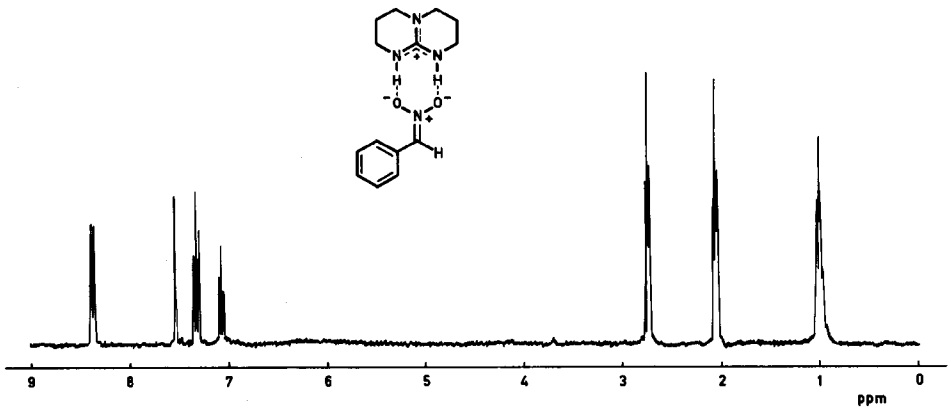


Figure 5.6 ^{1}*H-NMR spectrum of a 1:1 mixture of phenylnitromethane* **12f** *and TBD* **60**.

The downward shifts of the signals of the aromatic ring indicate a decrease of electron density around the aromatic ring. The signal of the two methylene protons (δ = 4.59) of **12f** fully disappear from the spectrum and a new singlet is formed (δ = 7.56). The chemical shifts of all methylene protons of the guanidinium cation are shifted upfield relative to non-protonated base. The positive charge is probably largely located at the two hydrogen atoms and not spread over the three nitrogen atoms as often indicated by the drawning of dotted lines. A preliminary conclusion points to the usefulness of NMR spectroscopy techniques for studying the complexes between nitroalkane substrates and bicyclic guanidine **60**.

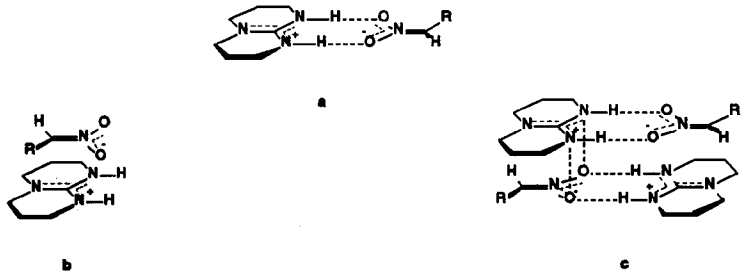


Figure 5.7 *Possible modes of complexations between the TBD* **60** *guanidinium cation and a nitronate anion* **8**.

NOE experiments,[15] revealing through space interactions, might give some insight into the mode of complexation. Several modes of complexation in solution are possible. Three of them are given in figure 5.7. A 'head to head' complexation (figure 5.7 **a**) would result in the absence of interactions between the hydrogens of the two ions. The sandwich like complex (figure 5.7 **b**) and layered structure (figure 5.7 **c**) might result in positive NOE interactions between the hydrogens of the anion and the cation. The NOE spectra of the 1:1 complex of phenylnitromethane **12f** and TBD **60** did not reveal any interaction between the methylene protons of the guanidinium moiety and the protons of the phenyl ring or the Cα proton. This argues against: the stacked **b** and sandwich **c** like structures. The NOE experiments underline the given 'head to head' like structure (figure 5.7 **a**) in a benzene solution.

V 2.3.2 Nitroalkanes and TBD mixtures at different ratios

The binding constants between two molecules bonded via hydrogen bonds, in the absence of a proton transfer, are reported to be determined from the chemical shift differences of the bonding hydrogens depending on different ratios of the two interacting molecules.[16]

Nitroethane **12b**, phenylnitromethane **12f**, 2-nitrobutane **12g** and ethyl α-nitropropionate **12h** have been used to study the complexation with TBD **60** in benzene d_6. The ^{1}H-NMR spectra of the mixtures of the four nitroalkanes and TBD **60** show independent signals for the free nitroalkane and the nitronate anion. Nitroethane **12b** and 2-nitrobutane **12g** are only partly deprotonated in a 1:1 mixture. Phenylnitromethane **12f** and ethyl α-nitropropionate **12h** are fully deprotonated when TBD **60** is available in excess (figure 5.9a). A spectrum of a 1:1 mixture of nitroethane **12b** and TBD **60** is shown (figure 5.8).

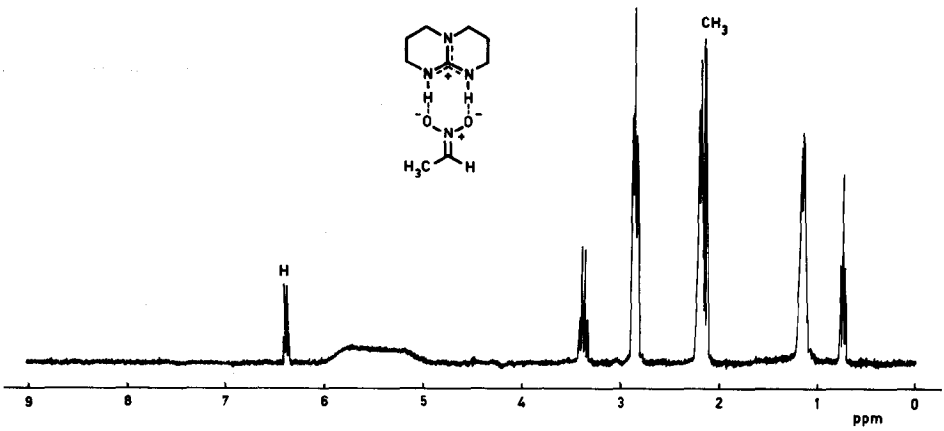


Figure 5.8 ^{1}*H-NMR spectrum of nitroethane* **12b** *and TBD* **60** *in a 1:1 mixture in* C_6D_6.

15 *The Nuclear Overhauser Effect in structural and Conformational Analysis*, Neuhaus, D., Williamson, M.; VCH Publ., Inc., New York, N.Y. 1989.

16 (a) Rebek, Jr., J., *Acc. Chem. Res.* **1984**, 17, 258. (b) Williams, K.; Askew, B; Ballester, P.; Buhr, C.; Kyu Sung Jeong; Jones, S. and Rebek, Jr., J., *J. Am. Chem. Soc.* **189**, 111, 1090.

In a 1:1 mixture of the TBD **60** and nitroethane **12b** (figure 5.8), at a 0.025 M concentration, 64 % of the nitroethane **12b** is deprotonated by the base. The signals of the remaining nitroethane are shown at δ=0.73 ppm (*t*, CH_3) and 3.37 ppm (*q*, CH_2), unchanged compared to the parent nitroethane **12b** compound. The nitronate anion gives distinct signals; the CH_3 signal has moved downfield to δ=2.13 ppm (*d*, CH_3) and has become a doublet. The Cα methine proton resonates at δ=6.41 ppm as a quartet. Two different N-H signals appear in the spectrum, indicating the protonated and the non-protonated guanidine base. The chemical shifts of the N-H protons depend on the ratios of the nitroalkane and TBD **60** as shown for nitroethane **12b** in figure 5.9b. The largest chemical shift is observed at an 1:1 ratio, indicating a one to one complex in solution.[17]

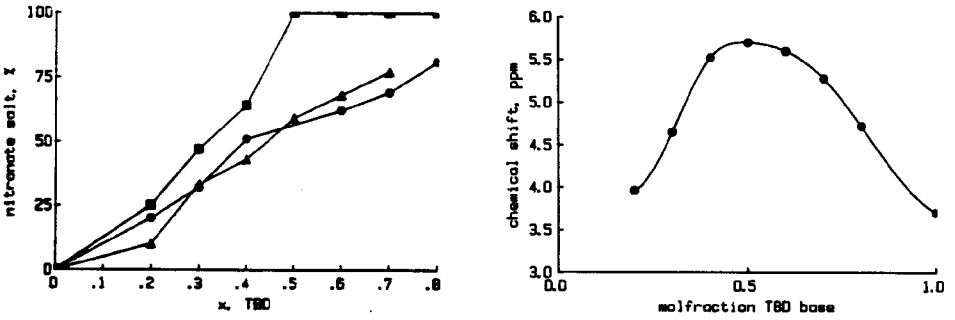


Figure 5.9 a. *The percentage of deprotonation against the nitroalkane/TBD ratio: nitroethane* **12b** (●); *2-nitrobutane* **12g** (▲); *phenylnitromethane* **12f** (■); *ethyl α-nitropropionate* **12h** (♦); *the plots of* **12f** *and* **12h** *coincide.* b. *The chemical shifts of the N-H protons at varying ratios of nitroethane* **12b** *and TBD* **60**.

Titration experiments,[17] to determine the binding constants between the nitroalkanes and TBD **60**, detected by ^{1}H-NMR techniques, are not possible because the mixtures do not result in an average signal of both the complexed and the non-complexed compounds. This indicates that the binding constants are too large to be measured by direct techniques. These large binding constants ensure a tight enough complex between substrate and catalyst. Therefore TBD **60** satisfies the demand for a large binding constant between the guanidine catalyst and the nitroalkane substrate.
Ethyl α-nitropropionate **12h** as a substrate revealed a somewhat different complexing behavior than the other three substrates with only a -NO_2 functional group. When **12h** or TBD **60** is present in at least a twofold excess, the spectra are comparable to the spectra of mixtures of the other nitroalkanes **12b**, **12f** and **12g** and TBD **60**. However, at about a 1:1 ratio, the clear structure of the spectrum disappeared. This probably resulted from an average of more then one mode of complexation. It illustrates the ambident character of ethyl α-nitropropionate as a substrate. The negative charge of the

17 (a) Williams, K.; Askew, B; Ballester, P.; Buhr, C.; Kyu Sung Jeong; Jones, S. and Rebek, J., Jr., *J. Am. Chem. Soc.* **1989**, 111, 1090 and references therein. (b) Rebek, Jr., J., *Acc. Chem. Res.* **1984**, 17, 258.

ethyl α-nitropropionate anion is probably divided over all electronegative atoms in the molecule (figure 5.10), creating more than one binding site for the guanidinium cation.

Figure 5.10 *Charge delocalisation in the anion of ethyl α-nitropropionate* **12h**.

The nitroester **12h** is therefore not an ideal compound for testing the validity of the guanidine structure as an anchor for nitroalkane substrates. The unclear mode of complexation between ethyl α-nitropropionate and TBD **60**, along with the clear complexation behavior between TBD **60** and e.g. phenylnitromethane **12f**, underlines the validity of the proposed mode of complexation (figure 5.1).

V 2.4 Crystallization experiments

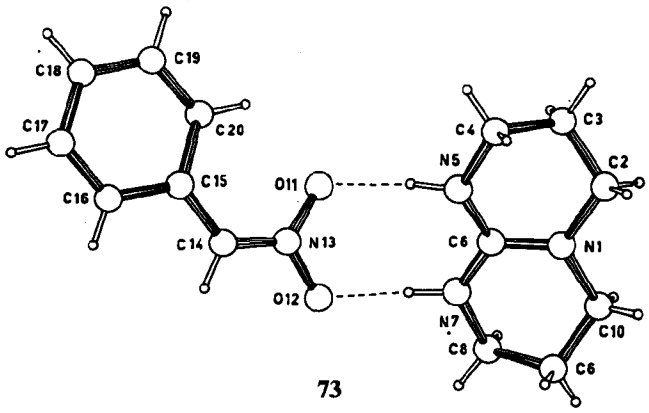
The nitroalkanes and TBD **60** form salts in solution. Crystallization of a complex to obtain a single crystal followed by an X-ray structure determination might provide definite proof of the mode of complexation between substrate and catalyst, at least in the solid state.
The aromatic[18] nitroalkane, phenylnitromethane **12f** forms an almost flat nitronate anion after deprotonation. In principle, **12f** seemed a good candidate for crystallization experiments. Toluene was the solvent of choice for crystallization experiments; the salt concentration in toluene should be kept between 0.025 and 0.1 M. *n*-Pentane was added to induce crystallization at low enough concentrations. Single crystals suitable for an X-ray structure determination were obtained from 7 ml of toluene containing 0.25 mmol of the salt (a 0.036 M solution) to which 4 ml of *n*-pentane was added. The solution was kept in a closed tube and was warmed, to a maximum of 50 °C, until a clear solution was obtained. The closed tube was left at room temperature. Crystals were formed after 5 days. The crystals turned somewhat dull when exposed to air and seemed somewhat hygroscopic. An X-ray crystal structure analysis of the monoclinic crystals revealed the structure of the salt complex **73** (figure 5.11).[19] A paper by Davis and co-workers,[20] dealing with essentially the same chemistry, was published at the same time as our paper. The crystal structure **73** confirms the proposed 'head to head' binding mode (figure 5.1) between the nitronate anion and the guanidinium cation. The 'head to head' orientation in **73** satisfies the demand for a tight and predictable complexation between the catalyst and the nitroalkane substrate.

---

18 Aromatic groups are often used to obtain crystalline derivatives of compounds. 2,4-Dinitro phenylhydrazone (Buckinham, Q., *Chem. Rev., Chem. Soc.*, **1969**, 23, 37) and 4-biphenyl dialkyl silyl chlorides (Anthony, J. and Diederich, F., *Tetrahedron Lett.* **1991**, 32, 3787) are used to obtain crystalline derivatives of carbonyl or hydroxy compounds.

19 van Aken, E.; Wynberg, H and van Bolhuis, F., *J. Chem. Soc., Chem. Commun.* **1992**, 629.

20 Boyle, P.H.; Convery, M.A.; Davis, A.P.; Hosken, G.D. and Murray, B.A., *J. Chem. Soc., Chem. Commun.* **1992**, 239.



73

Figure 5.11 The crystal structure of the TBD/phenylnitromethane salt **73**.

Table 5.5 *Bond distances for* **73** *in Ångströms.*

Atom1	Atom2	Distance	Atom1	Atom2	Distance	Atom1	Atom2	Distance
O11	N13	1.310(2)	N7	C8	1.465(3)	C15	C20	1.413(3)
O12	N13	1.314(2)	N7	H7	0.79(3)	C16	C17	1.383(3)
N1	C2	1.472(3)	N13	C14	1.327(3)	C17	C18	1.391(3)
N1	C6	1.344(3)	C2	C3	1.510(40	C18	C19	1.397(3)
N1	C10	1.470(3)	C3	C4	1.527(4)	C19	C20	1.390(3)
N5	C4	1.464(3)	C8	C9	1.524(4)	O11	N5	2.792(2)
N5	C6	1.337(3)	C9	C10	1.516(4)	O12	N7	2.781(2)
N5	H5	0.83(3)	C14	C15	1.457(3)	O11	H5	1.97(3)
N7	C6	1.329(3)	C15	C16	1.421(3)	O12	H7	1.99(3)

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 5.6 *Bond angles of* **73** *in degrees.*

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C2	N1	C6	122.3(2)	O11	N13	C14	123.4(2)	N1	C10	C9	112.1(2)
C2	N1	C10	115.6(2)	O12	N13	C14	119.5(5)	N13	C14	C15	126.6(2)
C6	N1	C10	122.0(2)	N1	C2	C3	111.7(2)	C14	C15	C16	117.1(2)
C4	N5	C6	121.8(2)	C2	C3	C4	109.2(2)	C14	C15	C20	125.4(2)
C4	N5	H5	122.0(2)	N5	C4	C3	107.8(2)	C16	C15	C20	117.5(2)
C6	N5	H5	116.2(2)	N1	C6	N5	120.6(2)	C15	C16	C17	121.1(2)
C6	N7	C8	122.1(2)	N1	C6	N7	120.8(2)	C16	C17	C18	120.8(2)
C6	N7	H7	115.0(2)	N5	C6	N7	118.6(2)	C17	C18	C19	119.0(2)
C8	N7	H7	122.0(2)	N7	C8	C9	108.7(2)	C18	C19	C20	121.1(2)
O11	N13	O12	117.2(2)	C8	C9	C10	108.4	C15	C20	C19	120.5(2)

Numbers in parentheses are estimated standard deviations in the least significant digits.

The three nitrogen atoms and C_6 of the guanidinium moiety lie almost in one plane. The angle between the guanidinium moiety and the nitronate anion is about 40 degrees. The nitronate anion is nearly flat (figure 5.12). The guanidinium cation fixates the nitronate anion with the two geminal N-H hydrogen bonding donors. The projection as depicted in figure 5.12 shows the two enantiotopic sites of the α-phenylnitromethane nitronate anion. The incoming electrophile, from above or below, determines the stereochemistry on Cα in the addition product.

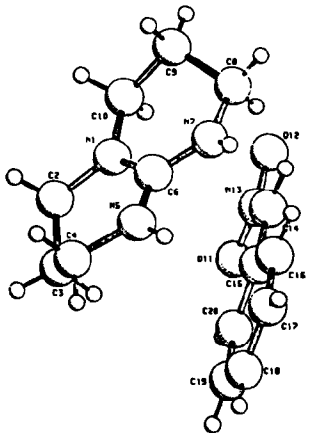


Figure 5.12 A side projection of the TBD/phenylnitromethane complex **73.**

The distances between C_4 and C_8 of the guanidinium moiety and Cα of the nitronate anion is about 0.6 nm (6 Å). With a chiral analog of TBD, substituted at C_4 and C_8, during the reaction this distance has to be bridged over to induce a difference between the two enantiotopic faces of the nitronate anion (see section I 3.1 and I 6.3). Introduction of two groups R at C_4 and C_8, likely to interact with the nitronate anion and/or with the incoming electrophile, might induce enantioselective nitroalkane addition reactions.
Attempts to obtain single crystals of salts of TBD **60** and other nitroalkanes were unsuccessful and resulted mainly in the separation of oils.

V 3 THE ACHIRAL BICYCLIC AMIDINE 61a AS A MODEL CATALYST

The pentamethylbicyclic amidine (PMBA) **61a**[21] was prepared and tested as a model catalyst. The synthesis of **61a** deserves some extra attention, both because of its elegance and its limitations. Amidine **61a** was prepared in an 30 % overall yield (figure 5.14).
The cyclization step of the amidine.HCl **68a** salt is beautiful on paper as well as at the bench. All four methyl groups (alkyl groups) are required to promote cyclization.[21] These alkyl groups activate the olefines just enough to induce the acid catalyzed cyclization. This limits the synthesis to α,α'-tetrasubstituted bicyclic amidines. The mechanism of the cyclization is unclear, but a nucleophilic addition of the two nitrogen atoms to the protonated olefines is suggested by the authors.
At the bench, in the cyclization step, one ends up with a black coal-like substance, hard as stone, at the bottom of the flask. Eschenmoser's experimentals do not reveal the need of shaking this flask with acid for more than three hours. The amidine **61a** was eventually isolated as a colorless oil in 75 % yield.

---

21 Heinzer, F.; Soukup, M. and Eschenmoser, A., *Helv. Chim. Acta* **1978**, 61, 2851.

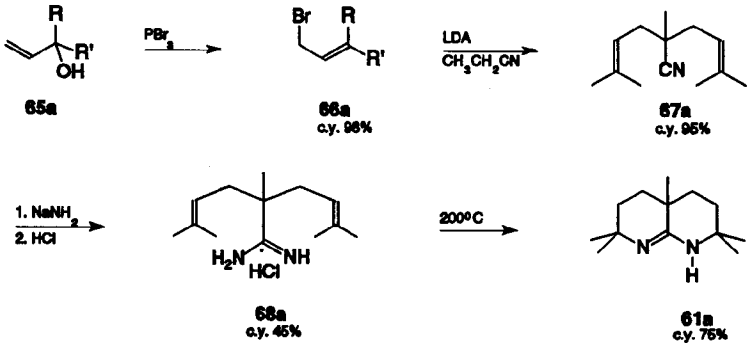


Figure 5.14 Eschenmoser synthesis of a bicyclic amidine **61a** *$R=R'=CH_3$.*

The bicyclic amidine **61a**, as a strong base like TBD **60**, is a very good catalyst under standard conditions. Its catalytic activity, relative to that of quinine **1a**, in standard reaction I is given in figure 5.15.

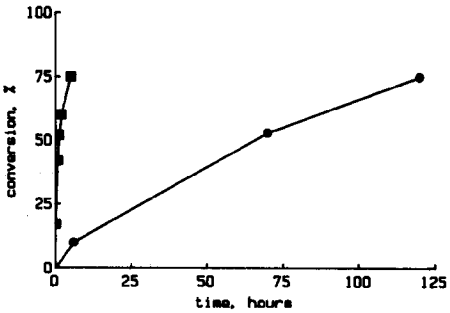


Figure 5.15 The catalytic activity of PMBA **61a** *(■) and quinine* **1a** *(●) in the standard reaction I compared.*

The bicyclic amidine **61a** racemizes the secondary nitroalkane Michael adduct **14b** under reaction conditions as does TBD **60**. The catalyst **61a** was tested under the same conditions as TBD **60** (section V 2.1). Nitroalkane Michael adduct **14b** was recovered in 79 % yield and had lost all optical activity.
The complexing ability of the amidine **61a** was not tested thoroughly. The 1:1 mixture of ethyl α-nitropropionate **12h** and **61a** resulted in complete deprotonation of the nitro compound, as shown by ^{1}H-NMR experiments. The amidine **61a** is thought to have enough space between the four methyl groups[21] to complex a nitronate anion.

solid with ethyl α-nitropropionate **12h** and hair-like crystals with phenylnitromethane **12f**, too thin for an X-ray crystal structure determination.

V 4 CONCLUDING REMARKS

Bicyclic guanidine TBD **60** and bicyclic amidine PMBA **61a** are very good catalysts in the nitroalkane addition reactions under standard conditions. Their solubility in toluene proved considerably higher than that of the cinchona alkaloids **1a-d**. More important, however, the mode of complexation between the bicyclic guanidine TBD **60** and a nitroalkane substrate, phenylnitromethane **12f** was established by an X-ray crystal structure determination. NMR spectroscopy experiments showed that the same 'head to head' mode of complexation probably exists in solution. TBD **60** and PMBA **61a** are therefore successful as model catalysts for the eventual chiral catalysts to be used in nitroalkane addition reactions.

V 5 EXPERIMENTAL SECTION

General. See experimental section chapter II section II 9. TBD **60** was used as purchased from Fluka. The allylic bromide **66d** was prepared quantitatively via a vinyl Grignard addition[22] to acetophenone and a 1,3 substitution of the allylic alcohol **65d**.[23] Linalool **65b** (Aldrich 97 %).

^{1}H-NMR complexation experiments All spectra were recorded on a Varian VXR-300. General procedure: Solutions of the nitroalkanes (**12b**, **12f**, **12g**, and **12h**) and the base TBD **60** in benzene d_6 at concentration of 0.05 mM were prepared. A nitroalkane and the TBD **60** solutions were mixed at ratios varying from 500 µl - 0 µl; 400 µl - 100 µl; 350 µl - 150 µl; 300 µl - 200 µl; 250 µl - 250 µl; 200 µl - 300 µl; 150 µl - 350 µl; 100 µl - 400 µl and 0 µl - 500 µl. ^{1}H-NMR spectra were recorded. The ratio's of the parent nitroalkane against the nitronate anion were determined by integration.
^{1}H-NMR NOE experiment The nitroalkane **12f** and the base TBD **60** were dissolved in benzene d_6, in equal amounts at a concentration of 0.05 mM, resulting in a salt concentration of 0.025 mM.

*TBD **60**/ethyl α-nitropropionate* **14h** *salt* Crystallization of the guanidinium/nitronate salt. The bicyclic guanidine TBD **60** (139.2 mg, 1.0 mmol) and ethyl α-nitropropionate **12h** (147.1 g, 1.0 mmol) were dissolved in 8 ml CH_2Cl_2. Diethyl ether (20 ml) was added. Very thin needles were formed. Slow crystallization in a Slenck apparatus also resulted in thin colorless needles; mp 121.3-122.9 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.27 ppm (s, 2H, 2N*H*), 4.18 (q, J=7.0Hz, 2H, OCH_2CH$_3$), 3.34 (t, J=5,9Hz, 4H, 2CH_2N), 3.27 (t, J=5.9Hz, 4H, 2CH_2N), 2.19 (s, 3H, CH_3C=NO$_2$), 1.98 (p, J=6.2Hz, 4H, CH$_2$$CH_2CH_2$), 1.28 (t, J=7.0Hz, 3H, CH_3CH$_2$O); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 59.2 ppm (t), 46.6 (2t), 37.5 (2t), 20.6 (2t), 14.8 (q), 14.3 (q); IR (KBr, pellet): ν 3216 cm^{-1} (m), 3149 (m), 3041 (m), 2974 (m), 2878 (m), 2303 (w), 1693 (m), 1649 (s), 1558 (m), 1437 (m, br), 1367 (m), 1322 (s), 1260 (sh), 120-2 (w), 1161 (w), 1093 (s), 1020 (w), 955 (w), 887 (w); anal. calcd. for $C_{12}H_{22}N_4O_4$: C 50.34, H 7.74, N 19.57, found: C 49.38, H 7.74, N 18.92.

*TBD **60**/phenylnitromethane* **12f** *salt* **73** TBD **60** (0.139 g, 1.0 mmol) and phenylnitromethane **12f** (0.137 g, 1.0 mmol) were each dissolved in toluene (10 ml). The two clear solutions were joined and no salt precipitated. Part of this solution (5 ml, 0.25 mmol salt) was added in a tube. *n*-Pentane (4 ml) was added and some salt precipitated as an amorphous solid. An additional amount of toluene (2 ml) was added.

---

22 (a) Marvel, C.S. and Woolford, R.G., *J. Org. Chem.* **1958**, 23, 1658. (b) Seyfarth, D.and Stone, F.G.A., *J. Am. Chem. Soc.* **1957**, 79, 515.

23 Isler, O.; Gutmann, H.; Lindlar, H.; Montavon, M.; Rüegg, R.; Ryser, G. and Zeller, *Helv. Chim. Acta* **1956**, 39, 471.

The tube was stoppered and the solution was warmed carefully untill all solid material had re-solved. The tube was left at r.t. After 5 days crystals had formed, suitable for an X-ray crystal structure determination; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 ppm (d, J=8.1, 2H, N*H*), 7.5-7.1 (m, 6H, Ar*H*, C*H*NO_2), 2.88 (t, J=11.5, 4H, 2CH_2), 2.34 (t, J=11.5, 4H, 2CH_2), 1.12 (p br, J=5.9, 4H, 2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.66 ppm (s), 129.07, 128.87, 127.78, 126.17, 125.06 (*Ar*, *C*α), 46.12 (t), 37.47 (t), 20.65 (t); IR (CH_2CCl_2, solution): ν 3044 cm^{-1} (m), 2974 (m), 2879 (m), 2687 (w), 2303 (w), 1758 (m), 1713 (s), 1653 (s), 1555 (s), 1405 (m), 1373 (m), 1322 (m), 1243 (m), 1185 (w), 1071 (w), 887 (w), 668(w)

X-ray crystal structure **73** The crystal, with approximate dimensions of 0.45 x 0.35 x 0.20 mm, was mounted in a random orientation on a glass fiber. Preliminary examination and data collection were performed with Mo K radiation (λ = 0.71073 Å) on a Nonius CAD4F computer, controlled kappa axis diffractometer equiped with a graphite crystal, incident beam monochromator and interfaced to a PDP11/23. Cell constants and an orientation matrix for the data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range 7.2° $\leq$ 0 $\leq$ 24.8°, measured by a computer controlled slit method of centering. *Crystal data* for **73** at 130 K $C_7H_{14}N_3.C_7H_6NO_2$, *Mr* = 276.34, monoclinic, space group $P2_1/a$, a = 10.338(2), b = 10.627(2), c = 13.232(3) Å, ß = 93.95(2)° and V = 1456.2 Å^3, Z = 4, D_c = 1.266 g cm^{-3}, λ = 0.71073 Å, μ(Mo-Kα) = 0.82 cm^{-1}. Final R = 0.041 and R_w = 0.048 for 2470 reflections. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

1-Bromo-2-methyl-2-butene **66a** The allylic bromide **66a** was prepared on a 0.5 molar scale according to a described procedure.[24] Distillation of the crude product yielded the allylic bromide **66a** in 94 % yield as a slightly colored oil; bp 58 °C at 51 mmHg (lit. 59-60 °C at 60 mmHg).

2,5,8-Trimethyl-5-cyanonona-2,7-diene **67a** The di-olefinic nitrile **67a** was prepared on a 0.1 molar scale according to a described procedure.[21] Both starting materials were distilled prior to use. The crude product was stripped with 10 ml of toluene to remove the last traces of THF yielding 19,68 gr (103 mmol, 100 %) of the nitrile **67a**. Distillation (94 °C, 0.2 mmHg) yielded 13.67 gr (71 mmol, 71 %) of the purified product; the remaining high boiling fraction had apparently polymerized. ^{1}H-NMR (60 MHz, CCl_4): δ 5.23 ppm (t br, J=7.7, 2H, C*H*CH_2), 2.20 (d br, J=7.7, 4H, CH_2CH), 1.77 (s, 6H, 2CH_3), 1.63 (s, 6H, CH_3), 1.22(s, 3H, CH_3).

2,5,8-Trimethyl-5-amidinenona-2,7-diene **68a** Amidine **68a** was prepared on a 59 mmol scale according to a literature procedure.[21] It was obtained as a yellow oil 5.06 gr (24.3 mmol, 41 %) that solidified on standing. ^{1}H-NMR (60 MHz, CCl_4): δ 5.40 ppm (s, 3H, N_2H_3), 5.05 (t br, J=7.7, 2H, 2C*H*), 2.10 (d br, 4H, 2CH_2), 1.70 (s br, 6H, 2CH_3), 1.55 (s br, 6H, 2CH_3), 1.00 (s, 3H, CH_3); The amidine **68a** was used in the cyclization step as obtained.

3,3,6,9,9-Pentamethyl-2,10-diazabicyclo[4,4,0]-1-decene **61** The reaction, on a 24 mmol scale, was performed as described.[21] The bicyclic amidine **61a** was obtained as a colorless oil 3.69 gr (17.7 mmol, 74 %) after destillation; bp 60-65 °C at 0.05 mmHg (20cm vigreux); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.39 ppm (s br, 1H, N*H*), 1.69 (dt, J_1=3.8, J_2=13.7, 2H, 2 ½CH_2ax), 1.44 (dt, J=3.8, J=13.5, 2H, 2 ½CH_2ax), 1.28 (dt, J_t=3.3, J_d=13,2, 2H, 2 ½CH_2eq), 1.20 (dt, J_t=3.3, J_d=13.2, 2H, 2 ½CH_2eq), 1.15 (s, 3H, CH_3), 1.12 (s, 6H, 2CH_3), 1.08 (s, 6H, 2CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 161.6 ppm (s), 53.01 (s), 34.67 (t), 32.87 (q), 32.74 (t), 29.42 (q), 25.36 (q); IR (neat, KCl): ν 3330 (m, br), 2963 (s), 2933 (s), 2861 (m), 1641 (s), 1457 (m), 1384 (m), 1357 (m), 1332 (w), 1324 (w), 1264 (w), 1234 (m), 1181 (m), 1153 (s), 1064 (w), 1001 (w), 779 (w), 742 (w), 665 (w), 628 (m).

General procedure for the Henry reactions TBD **60** (0.05 mmol, 5 %) was dissolved in the nitroalkane (2.0 mmol, 2 eq.) and aldehyde (1.0 mmol) was added. The reactions were monitored by ^{1}H-NMR. The reactions were worked up after the given times by filtration over silica (Merck 60) and evaporation of the excess of reagents under diminished pressure. The higher boiling reagents **12e**, **12h** and **12f** were removed by evaporation using an oil pump and a bulb-to-bulb distillation apparatus. The aromatic aldehydes **69f**, **69g** and **67h** were removed by washing the crude reaction mixture with a half saturated $NaHSO_3$ to which 10 % ethanol was added. The nitro alcohol products were isolated by extraction with toluene, drying over $NaSO_4$ and evaporation of the solvent.

---

24 Simon, H.L.; Kaufmann, Ad., Jr. and Schinz, H., *Helv. Chim. Acta* **1946**, 29, 1137.

3-Nitro-2-butanol **70a**; reaction time 3 min.; d.e.= %; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.49 ppm (m, 1H, C*H*NO_2), 4.34 (m, 1H, C*H*OH, erythro), 4.14 (m, 1H, C*H*OH, threo), 2.38 (d, J=, 1H, O*H*, erythro), 2.30 (d, J=, 1H, O*H*, threo), 1.54 (m, 3H, CH_3CHNO$_2$), 1.27 (m, 3H, CH_3CHOH).

2-Nitro-3-hexanol **70b**; reaction time 3 min.; d.e.=13 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.49 ppm (m, 1H, C*H*NO_2), 4.15 (m, 1H, C*H*OH, erythro), 3.87(m, 1H, C*H*OH, threo), 2.71(s br, 1H, O*H*), 1.50(d, J=, 3H, CH_3CHNO$_2$), 1.40 (m, 4H, CH_2CH_2), 0.91 (t, J=, 3H, CH_3CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 87.71 & 86.27 ppm (2d), 72.49 & 71.72 (2d), 34.94 & 34.75 (2t), 18.76 & 18.17 (2t), 15.91 & 13.57 (2q), 13.53 & 12.08 (2q); IR (neat, KCl): ν 3448 cm^{-1} (m, br), 2963 (s), 2876 (m), 1551 (s), 1456 (m), 1392 (s), 1361 (s), 1296 (m), 1252 (w), 1111 (m), 1063 (w), 1018 (m), 972 (m), 897 (w), 869 (w), 849 (w).

2-Nitro-3-heptanol **70c**; reaction time 3 min.; d.e.=11 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.54 ppm (m, 1H, C*H*NO_2), 4.19 & 3.91 (2m, 1H, C*H*OH), 2.2.31 & 2.20 (2d, J=6.8, 1H, O*H*), 1.55 (dd, J=2.2, J=6.8, 3H,CH_3CHNO$_2$), 1.60-1.25 (m, 6H, $CH_2CH_2CH_2$), 0.91 (t, J=7.1, 3H, CH_3CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 87.65 & 86.24 ppm (2d), 72.76 & 71.98 (2d), 32.60 & 32.48 (2t), 27.69 & 27.07 (2t), 22.28 & 22.24 (2t), 16.00 & 12.13 (2q), 13.72 (1q); IR (neat, KCl): ν 3447 cm^{-1} (m, br), 2959 (s), 2875 (m), 1550 (s), 1456 (m), 1392 (m), 1360 (m), 1296 (w), 1110 (w), 1032 (w), 1009 (w), 980 (w), 910 (w), 873 (w).

4-Nitro-2-methyl-1-pentanol **70d**; reaction time 10 min.; d.e.=17 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.67 ppm (m, 1H, C*H*NO_2), 3.98 & 3.69 (2m, 1H, C*H*OH), 2.20 (s br, 1H, O*H*), 1.78 & 1.65 (2m, 1H, C*H*CH_3), 1.55 (d, J=6.6, 3H, CH_3CHNO$_2$), 1.05 (dd, J=6.6, J=4.6, 3H, CH_3CH), 0.93 (d, J=6.8, 3H, CH_3CH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 86.19 & 84.46 ppm (2d), 77.14 & 76.98 (2d), 30.62 & 29.50 (2d), 19.55, 18.60, 18.30, 16.11, 15.05 & 11.75 (6q); IR (neat, KCl): ν 3436 cm^{-1} (m, br), 2987 (m), 2943 (w), 1547 (s), 1450 (m), 1392 (m), 1363 (m), 1294 (m), 1270 (sh), 1155 (w), 1122 (m), 1103 (m), 1042 (w), 1008 (w), 986 (w), 968 (w), 918 (m), 894 (m); MSCI (CH_4): 148 (M+1).

4-Nitro-2,2-dimethyl-1-pentanol **70e**; reaction time 18 hr.; d.e.=31 %; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.49 ppm (m, 1H, C*H*NO_2), 4.15 (m, 1H, C*H*OH, erythro), 3.87 (m, 1H, C*H*OH, threo), 2.71 (s br, 1H, O*H*), 1.50 (d, J=, 3H, CH_3CHNO$_2$), 1.40 (m, 4H, CH_2CH_2), 0.91 (t, J=, 3H, CH_3CH_2).

2-Nitro-1-phenyl-1-propanol **70f**; reaction time 5 min.; d.e.=25 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38 ppm (m, 5H, Ar*H*), 5.40 (t, J=3.1, 1H, C*H*OH, erythro), 5.03 (dd, J=9.2, J=2.4, 1H, C*H*OH, threo), 4.82-4.66 (m, 1H, C*H*NO_2), 2.72 (d, J=3.2, 1H, O*H*, erythro), 2.60 (d, J=3.2, 1H, O*H*, threo), 1.50 (d, J=6.8, 3H, CH_3CHNO$_2$, erythro), 1.32 (d, J=6.8, 3H, CH_3CHNO$_2$, threo); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 138.59 ppm (s), 129.34 & 129.20, 128.92 & 128.69, 127.18 & 126.21 (2x3d), 88.68 & 87.68 (2d), 76.44 & 74.18 (2d), 16..6.1 & 12.30 (2q); IR (neat, KCl): ν 3533 cm^{-1} (m, br), 3066 (w), 3033 (w), 2995 (w), 2943 (w), 2905 (w), 1550 (s), 1493 (w), 1452 (m), 1388 (m), 1360 (m), 1291 (w), 1201 (w), 1134 (w), 1051 (m), 1021 (m), 992 (w), 907 (w), 869 (w), 765 (s), 702 (s); HRMS calc. for $C_9H_{11}NO_3$: 181.074; found: 181.073.

2-Nitro-1-furyl-1-propanol **70g**; reaction time 15 min.; d.e.=42 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ ppm (dd, J=0.8, J=2.0, 1H, Ar*H*(4)), 6.40 (m, 2H, Ar*H*), 5.35 (d, J=4.2, 1H, C*H*OH, erythro), 5.08 (d, J=8.8, 1H, C*H*OH, threo), 4.98 & 4.84 (2m, 1H, C*H*NO_2), 2.63 (s br, 1H, O*H*), 1.61 (d, J=6.8, CH_3CHNO$_2$, erythro), 1.40 (d, J=6.8, CH_3CHNO$_2$, erythro); ^{13}C-NMR(75 MHz, $CDCl_3$): δ 151.14 & 150.56 ppm (2s), 143.14 & 142.63 (2d), 110.44 & 110.37 (2d), 109.22 & 107.98 (2d), 86.16 & 84.80 (2d), 69.23 & 68.71 (2d), 15.96 & 12.95 (2q); IR (neat, KCl): ν 3427 cm^{-1} (m, br), 2993 (m), 2946 (w), 2905 (w), 1550 (s), 1502 (w), 1450 (w), 1391 (m), 1362 (m), 1292 (w), 1231 (w), 1150 (m), 1049 (m), 1012 (m), 950 (w), 933 (w), 903 (w), 883 (w), 870 (w), 822 (w), 746 (m), 702 (w); HRMS, calcd. for $C_7H_9N_4$: 171.053, found: 171.053; MSCI (NH_3): 189 (M+18), 206 (M+35).

2-Nitro-1-(o-hydroxyphenyl)-1-propanol **70h**; reaction time 18 days; d.e.= 40 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60-6.90 ppm (m, 4H, Ar*H*), 5.59 (d, J=3.1, 1H, C*H*OH, erythro), 6.16 (d, J=9.5, 1H, C*H*OH, threo), 5.02 (m, 1H, C*H*NO_2, erythro), 4.80 (m, 1H, C*H*NO_2, threo), 3.59 (m br, 1H, O*H*), 1.60 (d, J=6.8, 3H, CH_3CHNO$_2$, erythro), 1.1.35 (d, J=6.8, 3H, CH_3CHNO$_2$, threo); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 154.67 ppm (s), 130.23 & 129.60 (2d), 128.96 & 127.52 (2d), 122.37 (s), 120.50 & 119.83 (2d), 117.06 & 116.80 (2d), 86.47 & 86.20 (2d), 76.23 & 74.09 (2d), 16.63 & 12.20 (2q); IR (neat, KCl): ν 3392 cm^{-1} (m, br), 2995 (w), 2943 (w), 1662 (w), 1642 (w), 1608 (w), 1596 (w), 1549 (s), 1488 (w), 1457 (m), 1389 (m), 1361 (m), 1238 (m), 1184 (w), 1151 (w), 1108 (w), 917 (w), 870 (w), 757 (m); HRMS, calc. for $C_9H_{11}NO_4$: 197.069, found: 197.069.

1-Nitro-2-hexanol **71a**; reaction time 15 min.; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.46-4.25 ppm (m, 3H, $CHCH_2NO_2$), 2.54 (m, 1H, O*H*), 1.65-1.29 (m, 6H, $CH_2CH_2CH_2$), 0.92 (t, J=7.1, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.56 ppm (t), 68.54 (d), 33.23 (t), 27.01 (t), 22.12 (t), 13.58 (q); IR (neat, KCl): ν 3520 cm^{-1} (sh), 3435 (m, br), 2959 (s), 2935 (s), 2873 (m), 1554 (s), 1467 (m), 1419 (m), 1380 (s), 1286 (m), 1199 (m), 1132 (m), 1089 (m), 1042 (m), 908 (w), 877 (w), 789 (w), 729 (w); MSCI (CH_4), 148 (M+1).

2-Nitro-3-heptanol **71b**; reaction time 15 min.; d.e.=11 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.52 ppm (m, 1H, $CHNO_2$), 4.18 & 3.90 (2s, 1H, *CH*OH), 2.27 & 2.20 (2m br, 1H, O*H*), 1.56 (dd, J=7.0, J=2.2, 3H, CH_3CHNO_2), 1.60-1.30 (m, 6H, $CH_2CH_2CH_2$), 0.92 (t, J=7.1, 3H, CH_3CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 87.58 & 86.17 ppm (2d), 72.68 & 71.93 (2d), 32.51 & 32.35 (2t), 27.60 & 26.98 (2t), 22.15 (t), 15.87 & 12.00 (2q), 13.63 (q); IR (neat, KCl): ν 3520 cm^{-1} (sh), 3440 (m, br), 2958 (s), 2873 (m), 1714 (w, br), 1550 (s), 1456 (m), 1391 (s), 1295 (m), 1205 (w), 1112 (m), 1031 (m), 1007 (m), 979 (m), 917 (w), 873 (m), 791 (w), 731 (w), 686 (w); MSCI (CH_4), 162 (M+1).

3-Nitro-4-octanol **71c**; reaction time 15 min.; d.e.=13 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.37 ppm (m, 1H, $CHNO_2$), 4.03 & x.xx (2m, 1H, *CH*OH), 2.40-1.30 (m, 9H, O*H*, CH_2CHNO_2, $CH_2CH_2CH_2$), 0.93 (m, 6H, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 94.29 & 93.75 ppm (2d), 72.01 & 71.64 (2d), 32.83 & 32.62 (2t), 23.54, 22.18, 22.12 & 21.32 (2x2t), 13.60 (q), 9.89 (q); IR (neat, KCl): ν 3520 cm^{-1} (sh), 3455 (m, br), 2959 (s), 2938 (s), 2874 (m), 1549 (s), 1459 (m), 1440 (m), 1377 (m), 1343 (), 1307 (w), 1262 (w), 1129 (w), 1092 (w), 1051 (w), 1019 (m), 969 (w), 924 (w), 901 (w), 889 (w), 850 (w), 809 (m), 731 (w); MSCI (CH_4), 162 (M+1).

4-Nitro-5-nonanol **71d**; reaction time 15 min.; d.e.=27 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.47 ppm (m, 1H, $CHNO_2$), 4.01 (m, 1H, *CH*OH, erythro), 3.85 (m, 1H, *CH*OH, threo), 2.36-1.27 (m, 11H, O*H*, $CH_2CH_2CHNO_2$, $CH_2CH_2CH_2$), 0.94 (m, 6H, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 92.56 & 91.92 ppm (2d), 72.16 & 71.89 (2d), 32.95 & 32.63 (2t), 32.12 & 29.77 (2t), 27.50 & 27.13 (2t), 22.26 & 22.18 (2t), 19.06 & 18.79 (2t), 13.60, 13.21 & 13.17 (3q); IR (neat KCl): ν 3520 cm^{-1} (sh), 3444 (m, br), 2962 (s), 2935 (s), 2875 (m), 1710 (w, br), 1551 (s), 1465 (m), 1436 (m), 1379 (m), 1286 (w), 1238 (w), 1120 (m), 1040 (m), 1008 (w), 902 (w), 854 (w), 761 (w), 730 (w); MSCI (CH_4), 190 (M+1).

2-Methyl-4-nitro-5-nonanol **71e**; reaction time 15 min.; d.e.=24 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.56 ppm (m, 1H, $CHNO_2$), 4.01 & 3.93 (2m, 1H, *CH*OH), 2.34-2.03 (m, 2H, O*H*, $CHCH_3$), 1.60-1.23 (8H, CH_2CHNO_2, $CH_2CH_2CH_2$), 0.95 (m, 9H, $3CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 91.12 & 90.37 ppm (2d), 72.48 & 72.34 (2d), 39.04 & 36.53 (2t), 33.08 & 32.60 (2t), 27.55 & 27.13 (2t), 24.91, 22.93, 22.83, 21.06, 20.98 & 13.69, 13.21 & 13.17 (2x3q), 22.26 (t); IR (neat, KCl): ν 3520 cm^{-1} (sh), 3447 (m, br), 2961 (s), 2873 (m), 1710 (w, br), 1550 (s), 1468 (m), 1433 (m), 1370 (m), 1291 (m), 1240(w), 1172 (w), 1125 (m), 1077 (m), 1050 (m), 950 (w), 923 (w), 900 (w), 852 (m), 818 (w), 788 (w), 731 (w); MSCI (CH_4), 204 (M+1).

1-Nitro-1-phenyl-2-hexanol **71f**; reaction time 1 day; d.e.=70 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 & 7.43ppm (2m, 5H, Ar*H*), 5.33 (d, J=9.9, 1H, $CHNO_2$), 4.56 (m, 1H, *CH*OH), 2.44 & 2.17 (2s br, 1H, O*H*), 1.57-1.16 (m, 6H, $CH_2CH_2CH_2$), 0.90 & 0.82 (2t, J=7.1 & J=7.1, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 131.92 & 131.66 ppm (2s), 129.98 & 129.79 (2d), 129.02 & 128.73 (2d), 127.95 (d), 96.70 & 93.90 (2d), 72.34 & 71.89 (2d), 32.87 & 31.75 (2t), 27.29 & 26.86 (2t), 22.18 & 22.05 (2t), 13.61 (q); IR (neat, KCl): ν 3315 cm^{-1} (m, br), 3069 (m), 2954 (m), 2856 (m), 1699 (w, br), 1544 (s), 1496 (w), 1466 (m), 1453 (m), 1363 (m), 1296 (w), 1275 (w), 1256 (w), 1130 (w), 1071 (w), 1055 (w), 971 (w), 928 (w), 891 (w), 873 (w), 788 (w), 732 (m), 696 (m), 664 (w).

3-Methyl-3-nitro-4-octanol **71g**; reaction time 1 day; d.e.=20 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.04 & 3.92 ppm (2m, 1H, *CH*OH), 2.30-1.20 (m, 9H, O*H*, $CH_3CH_2CNO_2$, $CH_2CH_2CH_2$), 1.50 & 1.49 (2s, 3H, CH_3NO_2, 0.89 (m, 6H, $2CH_3CH_2$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 93.31 & 95.11 ppm (2s), 76.19 & 775.31 (2d), 31.23 (t), 30.40 & 28.91 (2t), 28.50 (t), 22.44 (t), 17.35 & 16.31 (2q), 13.90 (q), 8.00 (q); IR (neat, KCl): ν 3520 cm^{-1} (sh), 3456 (m, br), 2957 (s), 2872 (m), 1710 (w, br), 1533 (s), 1458 (m), 1389 (m), 1353 (m), 1282 (w), 1201 (w), 1145 (w), 1120 (m), 1081 (m), 1040 (w), 1005 (m), 925 (w), 903 (w), 864 (w), 814 (w), 732 (w).

2-Methyl-2-nitro-3-hydroxy ethylheptanoic acid **71h**; reaction time 1 day; d.e.= 22 %; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.28 ppm (m, 2H, CH_2O), 3.25 (s, br, 1H, O*H*), 2.34 (m, 1H, *CH*OH), 1.75 (s, 3H, CH_3CNO_2), 1.6-1.2 (m, 6H, $CH_2CH_2CH_2$), 0.90 (m, 3H,CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.81 & 166.16 ppm (2s), 96.63 & 95.00 (2s), 74.20 & 73.31 (2d), 62.96 (t), 30.85 & 30.02 (2t), 28.17 & 28.09 (2t), 22.22

(t), 16.66 & 16.59 (2q), 14.01, 13.93, 13.81 & 13.71 (2x2q); IR (neat, KCl): ν 3544 cm^{-1} (m, br), 3480 (sh), 2958 (s), 2933 (s), 2873 (m), 1750 (s), 1553 (s), 1465 (m), 1451 (m), 1386 (m), 1369 (w), 1346 (m), 1298 (m), 1262 (m), 1203 (w), 1173 (w), 1142 (m), 1110 (m), 1039 (w), 1015 (m), 906 (w), 858 (w), 735 (w).

3-Methyl-1-nitro-2-butanol **72a**; reaction time 16 hrs.; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.45 ppm (m, 2H, CH_2NO_2), 4.10 (m, 1H, CHOH), 2.50 (s, 1H, OH), 1.80 (h, J=6.6, 1H, $CH(CH_3)_2$), 1.00 (dd, J=7.0, J=4.4, 6H, CH_3CH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 79.15 ppm (t), 73.22 (d), 31.53 (d), 18.10 (q), 17.19 (q); IR (neat, KCl): ν 3520 cm^{-1} (sh), 3444 (m, br), 2967 (s), 2937 (m), 2879 (m), 1713 (w, br), 1557 (s), 1468 (m), 1423 (m), 1383 (s), 1288 (m), 1257 (w), 1139 (m), 1207 (m), 1139 (m), 1068 (m), 1018 (m), 960 (w), 924 (w), 886 (m), 852 (w), 830 (w), 719 (sh).

4-Methyl-2-nitro-3-pentanol **72b**; reaction time 16 hrs.; d.e.=14 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.62 ppm (m, 1H, $CHNO_2$), 3.84 (m, 1H, CHOH), 2.60 & 2.49 (2s br, 1H, OH), 1.82-1.56 (m, 1H, $CH(CH_3)_2$), 1.51 (d, J=7.0, 3H, CH_3CHNO_2), 1.01 & 0.90 (dd, J=6.6, J=3.3 & dd, J=6.6, J=3.7, 6H, $(CH_3)_2CH$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 86.15 & 84.47 ppm (2d), 77.12 & 77.02 (2d), 30.62 & 29.53 (2d), 19.57, 18.63, 18.34, 16.15, 15.11 & 11.77 (3x2q); IR (neat, KCl): ν 3525 cm^{-1} (sh), 3465 (m, br), 2968 (s), 2879 (m), 1710 (w, br), 1549 (s), 1467 (m), 1452 (m), 1390 (s), 1366 (m), 1315 (w), 1295 (w), 1180 (w), 1139 (w), 1116 (w), 1989 (w), 1034 (w), 1006 (m), 987 (m), 965 (w), 883 (w), 868 (w), 826 (w), 682 (w); MSCI (CH_4), 148 (M+1).

2-Methyl-4-nitro-3-hexanol **72c**; reaction time 16 hrs.; d.e.=42 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.51 ppm (m, 1H, $CHNO_2$), 3.76 (t, J=9.8, 1H, CHOH, erythro), 3.63 (t br, J=12, 1H, CHOH, threo), 2.20 (s br, 1H, OH), 2.24-1.78 (m, 2H, CH_2CHNO_2), 1.72 (h, J=6.5, 1H, $CH(CH_3)_2$), 0.97 (m, 9H, $3CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 92.59 & 91.79 ppm (2d), 76.80 & 76.16 (2d), 30.33 & 30.01 (2d), 23.65 & 21.52 (2t), 19.46 & 19.03 (2q) 16.79 & 15.69 (2q), 10.25 & 9.95 (2q); IR (neat, KCl): ν 3534 cm^{-1} (m, br), 3480 (sh), 2968 (s), 2937 (m), 2881 (m), 1710 (w, br), 1551 (s), 1464 (m), 1438 (m), 1375 (m), 1340 (m), 1313 (m), 1263 (m), 1230 (w), 1180 (w), 1130 (m), 1089 (m), 1055 (w), 1004 (m), 945 (w), 925 (w), 887 (w), 866 (w), 831 (w), 805 (m), 676 (w), 612 (w); MSCI (CH_4), 148 (M+1).

2,6-Dimethyl-4-nitro-3-heptanol **72e**; reaction time 16 hrs.; d.e.=39 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.71 ppm (m, 1H, $CHNO_2$), 3.74 (m, 1H, CHOH, erythro), 3.59 (m, 1H, CHOH, threo), 2.30-1.45 (m, 5H, OH, $2CH(CH_3)_2$, CH_2CHNO_2), 0.97 (m, 12H, $2(CH_3)_2CH$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 89.46 & 88.34 ppm (2d), 77.36 & 76.67 (2d), 39.04 & 36.42 (2t), 30.36 & 29.97 (2d), 24.83, 23.09, 22.85, 20.96, 19.46, 18.87, 17.22 & 15.48 (2x4q); IR (neat, KCl): ν 3540 cm^{-1} (m, br), 3477 (m, br), 2963 (s), 2937 (sh), 2875 (m), 1710 (w, br), 1548 (s), 1468 (m), 1432 (w), 1370 (m), 1312 (w), 1293 (w), 1245 (w), 1172 (w), 1137 (w), 1066 (w), 1037 (w), 1002 (m), 960 (w), 942 (w), 922 (w), 852 (w), 682 (w); MSCI (CH_4), 148 (M+1).

3-Methyl-1-nitro-1-phenyl-2-pentanol **72f**; reaction time 6 days; d.e.=54 %; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.45 (m, 5H, ArH), 5.68 (d, J=7.5, $CHNO_2$, erythro), 5.45 (d, J=9.9, $CHNO_2$, threo), 4.49 (dd, J=2.2, J=9.9, CHOH, threo), 4.33 (t, J=7.5, CHOH, erythro), 2.2-1.1 (m, 2H, OH, $CH(CH_3)_2$), 1.0 (m, 6H, $(CH_3)_2CH$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 131.9 (s), 130-128.0 (Ar), 95.23 & 91.95 (2d), 76.40 & 75.92 (2d), 29.95 & 28.30 (2d), 21.70 & 19.91 (2q), 16.10 & 13.74 (2q); IR (neat, KCl): ν 3469 cm^{-1} (m, br), 3066 (w), 3034 (w), 2966 (m), 2876 (w), 1699 (w, br), 1601 (w), 1553 (s), 1523 (m), 1497 (w), 1453 (m), 1364 (m), 1331 (m), 1314 (w), 1268 (m), 1178 (w), 1136 (w), 1078 (w), 1002 (m), 945 (w), 921 (w), 874 (w), 708 (m), 695 (m), 631 (w).